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RESEARCH ARTICLE

Atypical Lymphocytes In Dengue Fever: Assessing Prognostic Value

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Abstract: ***Background:*** Identifying dengue patients at risk of developing complications early is crucial for guiding clinical management. There is currently no validated laboratory test for this purpose. Atypical lymphocytes are flagged as an abnormality during an automated Complete Blood Count (CBC). This study aims to assess the presence of atypical lymphocytes in severe dengue and evaluate their potential as a prognostic marker. ***Methods:*** We retrospectively collected data on 327 patients admitted with dengue fever at Saveetha Medical College and Hospital (SMCH) from October 2023 to April 2024. Laboratory data was extracted from the automated CBC analyzer. Patients included were serologically positive for dengue (Dengue NS1 or IgM). Exclusion criteria included patients under 18 years, pregnant women, and those with concomitant illnesses that may contribute to atypical lymphocytosis. Data analysis involved descriptive statistics and multi-variable linear regression using SPSS software version 29.0.2, with a p-value <0.05 considered statistically significant. ***Results:*** Out of 327 patients, 2.7% (n=9) had severe dengue, while 97.2% (n=318) had non-severe dengue. Among non-severe cases, 28.1% (n=89) had warning signs, and 69.1% (n=229) had no warning signs. Atypical lymphocytes were flagged in 100% of severe dengue cases, 78.6% of non-severe dengue cases with warning signs, and 46.7% of non-severe dengue cases without warning signs. ***Conclusion:*** Atypical lymphocytes were present in all severe dengue cases and in a significant proportion of non-severe cases with warning signs. However, their presence in nearly half of the non-severe cases without warning signs undermines their utility as a prognostic marker. Further studies are needed to establish their prognostic value, including post-hoc analyses to correlate atypical lymphocyte percentage with platelet count. Categories: Internal Medicine, Pathology, Microbiology, Community medicine

Keywords: Dengue fever, atypical lymphocytes, severe dengue, non-severe dengue.

INTRODUCTION

Dengue fever, a mosquito-borne viral infection caused by the dengue virus, poses a significant public health challenge, particularly in tropical and subtropical regions [1]. The disease manifests in a wide spectrum, from asymptomatic or mild febrile illness to severe forms, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Timely identification and management of patients at risk of developing severe dengue are critical to reduce morbidity and mortality [2][3]. However, predicting which patients will progress to severe disease remains challenging, and no validated laboratory test currently exists to reliably identify these high-risk patients early in the clinical course [4].

Atypical lymphocytes are characterized by their irregular size and shape, and basophilic cytoplasm, and are indicative of an activated immune response. Several studies have explored the role of atypical lymphocytes in the context of viral infections, including dengue, suggesting that their presence might correlate with disease severity [5][6].

The objective of this study is to assess the presence of atypical lymphocytes in severe dengue and establish their potential as a prognostic marker.

MATERIAL AND METHODS

Study Population and Setting:

This retrospective observational study was conducted at Saveetha Medical College and Hospital (SMCH), Chennai, India, from October 2023 to April 2024. We included 327 patients with serologically confirmed dengue fever (Dengue NS1 or IgM positive). Patients under 18 years, pregnant women, and those with concomitant illnesses contributing to atypical lymphocytosis were excluded.

This study has been approved by the Scientific Review Board of Saveetha Medical College and Hospital. Informed consent was waived, and researchers analysed only deidentified (anonymized) data. Records were obtained using the hospital's online database (Medical Information Archiving Software) and physical records, when required. We obtained demographic data, information on clinical symptoms or signs at presentation, and laboratory results during hospital

admission. All laboratory tests and management were performed at the discretion of the treating physician.

Study definition:
According to The World Health Organization (WHO), Dengue can be classified into two main categories: Non-severe Dengue (with or without warning signs) and severe dengue [2].

- Dengue without warning signs: includes symptoms such as fever, nausea, vomiting, rash, aches and pains, leukopenia, and a positive tourniquet test.
- Dengue with warning signs: includes additional symptoms like abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, and liver enlargement.
- Severe dengue: characterized by severe plasma leakage leading to shock or respiratory distress, severe bleeding, and severe organ impairment.

Data collection:
The medical records of patients were retrospectively reviewed and evaluated for the above mentioned clinical and laboratory parameters. Patients were classified into non-severe dengue (with or without warning signs) and severe dengue. Automated CBC analyzer was used to retrospectively assess the patients' blood sample data and look for atypical lymphocytes, which are flagged automatically if present.

Statistical analysis:
Statistical analysis was done using IBM SPSS Statistics software (version 29.0.2.0). Results are reported as means and percentages, as appropriate. No imputation was made for missing data. A p-value of <0.05 is taken as statistically significant.

RESULTS AND OBSERVATIONS:

Demographical, laboratory and clinical characteristics of the patients:
A total of 327 patients were considered for the study, consisting of 162 males (49.5%) and 165 females (50.5%), which has been illustrated in Figure 1. The mean age of the patients was 41.2 years, ranging from 18 to 65 years. Patients were classified into severe and non-severe dengue in accordance with the WHO classification criteria based on their laboratory and clinical parameters: Severe dengue was noted in 9 patients (2.7%), Non-severe dengue with warning signs was noted in 92 patients (28.1%) and non-severe dengue without warning signs was noted in 226 patients (69.1%). This has been illustrated further in Figure 2.

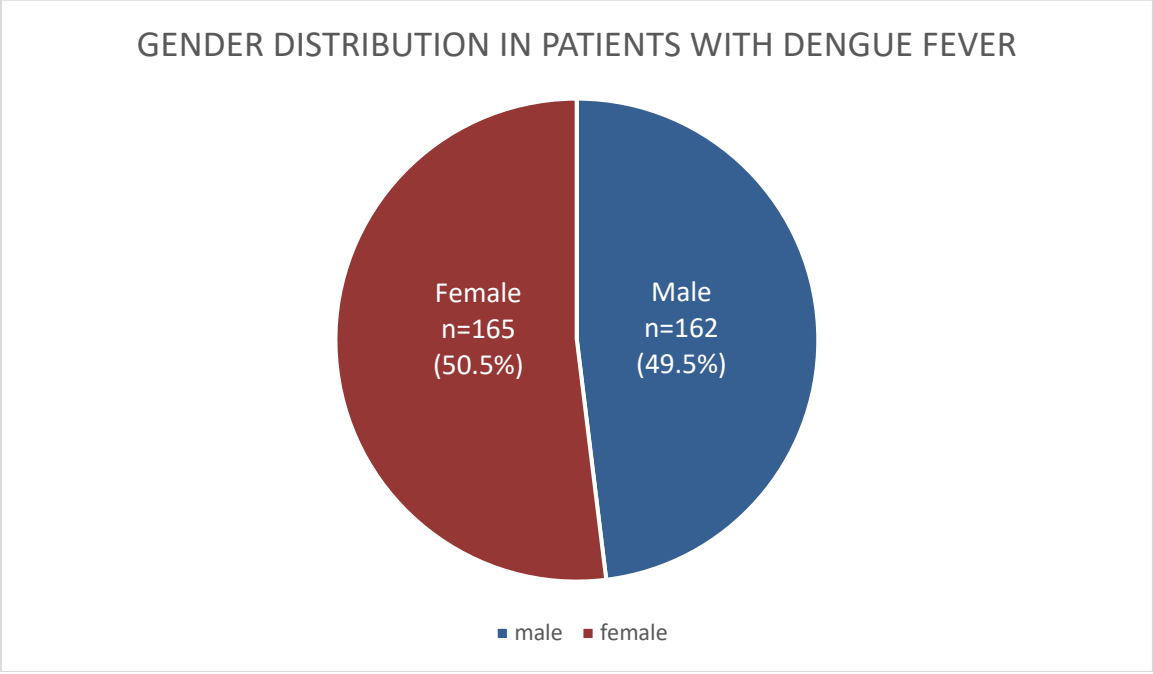
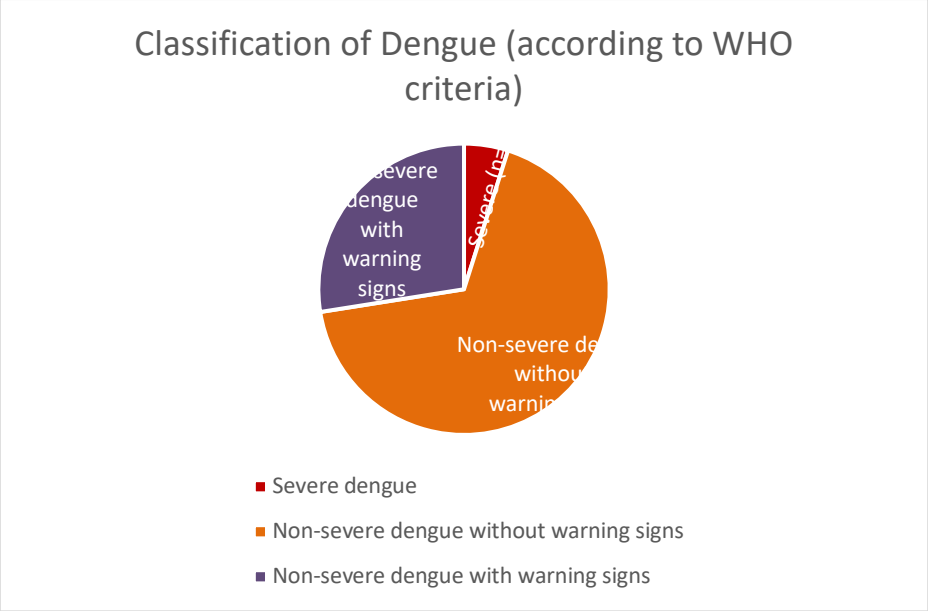


Figure 1: Gender distribution of Dengue patients included in this study



Laboratory Findings:

The mean platelet count among all patients was 150,000 platelets/µL, with a standard deviation of 50,000 platelets/µL. The presence of atypical lymphocytes varied significantly across the different dengue classifications.

Automated blood count analyser was utilized to access blood sample data retrospectively. Blood samples of the patient on date of admission were analysed for presence or absence of atypical lymphocytes. All severe dengue cases (100%) exhibited atypical lymphocytes. In non-severe dengue with warning signs, atypical lymphocytes were present in 78.6% of these cases. Non-severe dengue without warning signs showed atypical lymphocytes in 46.7% of these cases.

Figure 3 shows a box-and-whisker plot illustration comparing the presence and absence of atypical lymphocytes with platelet count. While there is a small difference in median platelet counts between the two groups, it is not very pronounced. The presence of atypical lymphocytes does not show a strong correlation with lower platelet counts. Both groups show a broad and overlapping range of platelet counts.

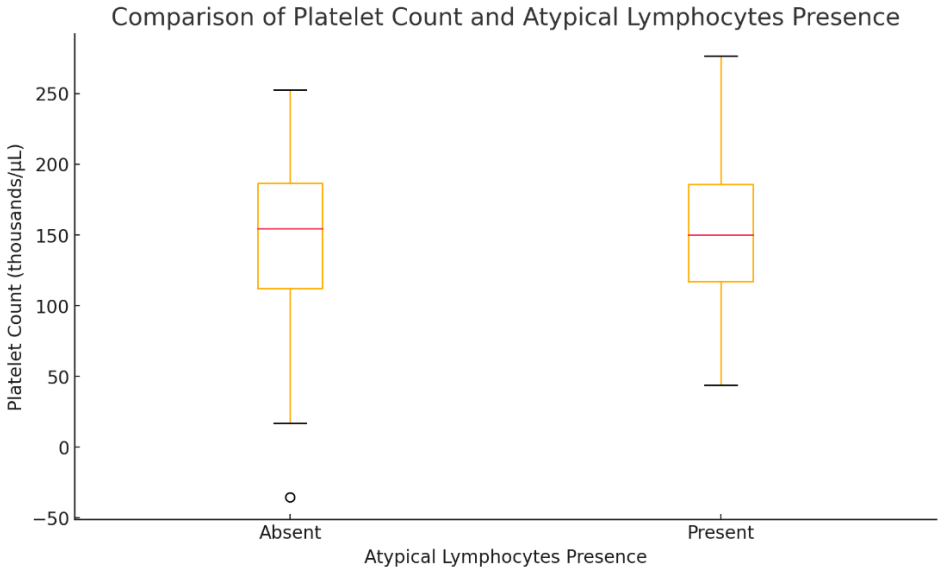


Figure 3: Box-and-whisker plot illustration showing the relationship between platelet count and atypical lymphocyte presence.

Statistical analysis:

1. *T-test for Platelet Count between Groups with and without Atypical Lymphocytes:*

Data highlighting the mean platelet count in the two groups has been given in Table 1.

ATYPICAL LYMPHOCYTE	Mean platelet count ± SD (per µL of blood)
Present	1,49,650 ± 46,363
Absent	1,50,517 ± 51,942

Table 1: Mean platelet count in patients grouped according to presence or absence of atypical lymphocytes

T-statistic was -0.159, P-value was 0.874.

The T-test results indicate that there is no statistically significant difference in the mean platelet count between patients with and without atypical lymphocytes (p-value > 0.05). The mean platelet counts for both groups are very similar, with overlapping standard deviations, further supporting the lack of a significant difference.

2. *Chi-square Test for Independence between Severity of Dengue and Presence of Atypical Lymphocytes*:

Chi-square statistic was 37.54, P-value was 0.00000000706.

This indicates a statistically significant association between the severity of dengue and the presence of atypical lymphocytes (p-value < 0.05). This suggests that the presence of atypical lymphocytes is **not independent** of the severity of dengue classification.

3. *ANOVA Test for Atypical Lymphocytes Presence across Different Dengue Classifications:*

F-statistic was 21.01, P-value was 0.00000000264.

This indicates a statistically significant difference in the presence of atypical lymphocytes across the different dengue classifications (p-value < 0.05).

4. *Kruskal-Wallis H-test for Non-parametric Comparison of Atypical Lymphocytes Presence across Different Dengue Classifications:*

H-statistic was 37.42, P-value was 0.00000000748

This also indicates a statistically significant difference in the presence of atypical lymphocytes across the different dengue classifications (p-value < 0.05).

Limitations of the study:

Retrospective collection of data may not capture all relevant variables or accurately reflect real-time clinical decision-making. Single-centric nature of the study limits its generalizability. The study period (October 2023 to April 2024) might not account for seasonal variations in dengue incidence and severity, which could influence the results. Although the sample size of 327 patients provides a substantial dataset, the number of severe dengue cases (9 patients) is relatively small. This may limit the statistical power to detect significant differences and draw robust conclusions. Variations in immune response could be a confounding factor.

DISCUSSION

This study aimed to evaluate the presence of atypical lymphocytes in dengue patients and their potential as a prognostic marker for disease severity. Our findings reveal that atypical lymphocytes are present in all severe dengue cases, and a significant proportion of non-severe cases with warning signs. However, their presence in nearly half of the non-severe cases without warning signs suggests limited utility as a sole prognostic marker. These results align with previous studies that have reported similar trends. For instance, a study by Phuong et al. (2016)[7] demonstrated a high prevalence of atypical lymphocytes in severe dengue cases, reinforcing their association with increased disease severity . Additionally, another study by Suvarna et al. (2018)[8] found that while atypical lymphocytes are indicative of an activated immune response, they are not exclusive to severe cases and can be observed in milder forms of the disease .

Recent research further supports our observations. A 2022 study by Gupta et al [9]. explored the prognostic value of various hematological parameters in dengue and highlighted that atypical lymphocytes, while significant, should be considered alongside other markers such as platelet count, hematocrit levels, and liver enzymes to accurately predict disease progression . Another study by Sharma et al. (2023)[10] emphasized the role of comprehensive clinical evaluation, suggesting that integrating atypical lymphocyte data with clinical symptoms and additional laboratory findings enhances predictive accuracy . Our study's limitations, including its retrospective design and single-center setting, underscore the need for multi-center, prospective research to validate these findings and develop reliable, multifactorial prognostic tools for dengue management. Overall, while atypical lymphocytes remain a relevant indicator, their prognostic value is maximized when used in conjunction with other clinical and laboratory assessments. Quantifying the proportion of atypical lymphocytes could also aid in assessing severity.

CONCLUSION:

This study investigated the presence of atypical lymphocytes in dengue patients and assessed their potential as a prognostic marker for disease severity. Our results indicate that while atypical lymphocytes are consistently present in all severe dengue cases and a significant proportion of non-severe cases with warning signs, their presence alone is insufficient as a reliable prognostic tool. Quantifying the proportion of atypical lymphocytes could provide more nuanced insights into their role in dengue pathogenesis and severity.

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